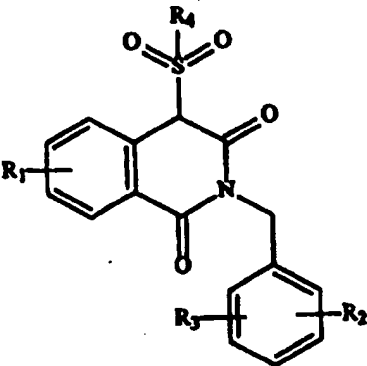
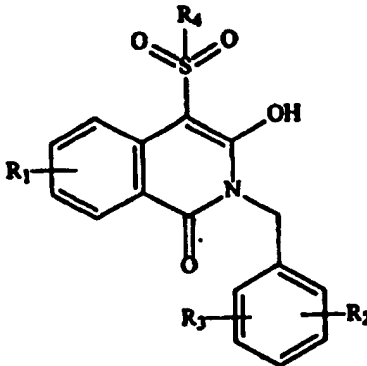




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 217/24, A61K 31/47	A1	(11) International Publication Number: WO 97/46532 (43) International Publication Date: 11 December 1997 (11.12.97)
<p>(21) International Application Number: PCT/US97/07980</p> <p>(22) International Filing Date: 13 May 1997 (13.05.97)</p> <p>(30) Priority Data: 60/019,131 3 June 1996 (03.06.96) US</p> <p>(71) Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. [US/US]; 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).</p> <p>(72) Inventors: LAZER, Edward, S.; 46 High Ridge Road, Trumbull, CT 06611 (US). CYWIN, Charles; 37 Quaker Ridge Road, Bethel, CT 06801 (US). SORCEK, Ronald, J.; 8D Beach Street, Bethel, CT 06801 (US).</p> <p>(74) Agents: RAYMOND, Robert et al.; Boehringer Ingelheim Corporation, 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).</p>		<p>(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: 2-BENZYL-4-SULFONYL-4H-ISOQUINOLIN-1,3-DIONES AND THEIR USE AS ANTI-INFLAMMATORY AGENTS</p>		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(IA)</p> </div> </div>		
<p>(57) Abstract</p> <p>Anti-inflammatory compounds of formula (I) or (IA) wherein R₁ is hydrogen, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy; R₂ and R₃ are the same or different and each is hydrogen, halogen, trifluoromethyl, C₁₋₄ alkyl, or C₁₋₄ alkoxy; and, R₄ is C₃₋₄ alkyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, trifluoromethyl, or nitro.</p>		

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2-BENZYL-4-SULFONYL-4H-ISOQUINOLIN-1,3-DIONES AND THEIR USE AS
ANTIINFLAMMATORY AGENTS

5 Field of the Invention

The invention relates to novel 2-benzyl-4-sulfonyl-4H-isoquinolin-1,3-diones and their use as antiinflammatory agents.

10 Background of the Invention

Many non-steroidal antiinflammatory drugs (NSAIDs) are currently marketed. They exert their antiinflammatory effect by inhibiting the enzyme cyclooxygenase. These drugs have a beneficial effect in reducing the pain and symptoms of inflammation but they have serious
15 unwanted side effects associated with their use, including gastrointestinal and renal toxicity. Recently a new isoform of cyclooxygenase (COX-2) has been discovered that is thought to be responsible for causing inflammation, and it is thought that much of the toxicity of current NSAIDS is due to their inhibition of COX-1. Most available NSAIDs are not selective in their inhibition of the two COX isoforms or are more potent in inhibiting COX-1.

20

Recently, there have been discovered agents which more or less selectively inhibit the COX-2 isoform. Exemplary of this new class of compounds is (meloxicam, UHAC62), which is described in U.S. Patent 4,233,299.

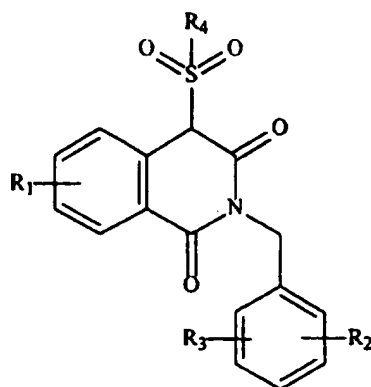
25 Summary of the Invention ¹

The present invention provides novel compounds having antiinflammatory activity which inhibit both COX-1 and COX-2 approximately equipotently or, in the case of certain preferred compounds, are more selective for COX-2.

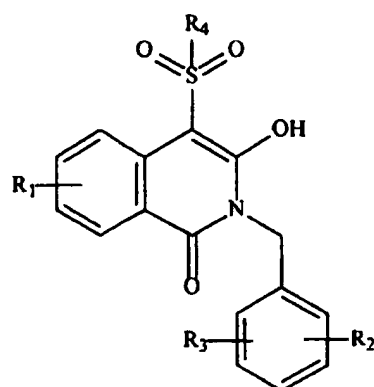
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Detailed Description of the Invention

In its broadest generic aspect, the invention comprises 2-benzyl-4-sulfonyl-4H-isoquinolin-1,3-diones of the formula I or IA



(I)



(IA)

wherein,

R₁ is hydrogen, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy;

R₂ and R₃ are the same or different and each is hydrogen, halogen, trifluoromethyl, C₁₋₄ alkyl, or C₁₋₄ alkoxy; and,

R₄ is C₃₋₄ alkyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, trifluoromethyl, or nitro.

It will be appreciated that formulas I and IA represent tautomeric forms of the same compound.

In a first subgeneric aspect, the invention comprises compounds of the above formula I or IA wherein,

R₁ is hydrogen, fluorine, chlorine, bromine, C₁₋₄ alkyl or C₁₋₄ alkoxy;

R₂ and R₃ are the same or different and each is hydrogen, fluorine, chlorine, bromine; trifluoromethyl, C₁₋₄ alkyl or C₁₋₄ alkoxy; and,

R₄ is isopropyl, t-butyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro.

5

In a second subgeneric aspect, the invention comprises compounds of the above formula I or IA wherein,

10 R₁ is hydrogen, or is in the 6- or 7-position and is fluorine, chlorine, bromine, C₁₋₄ alkyl or C₁₋₄ alkoxy;

R₂ and R₃ are the same or different and each is hydrogen, fluorine, chlorine, bromine; trifluoromethyl, C₁₋₄ alkyl or C₁₋₄ alkoxy; and,

15 R₄ is isopropyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro.

20 In a third subgeneric aspect, the invention comprises compounds of the above formula I or IA wherein,

R₁ is hydrogen, or is in the 6- or 7-position and is fluorine, chlorine, bromine, C₁₋₄ alkyl or C₁₋₄ alkoxy;

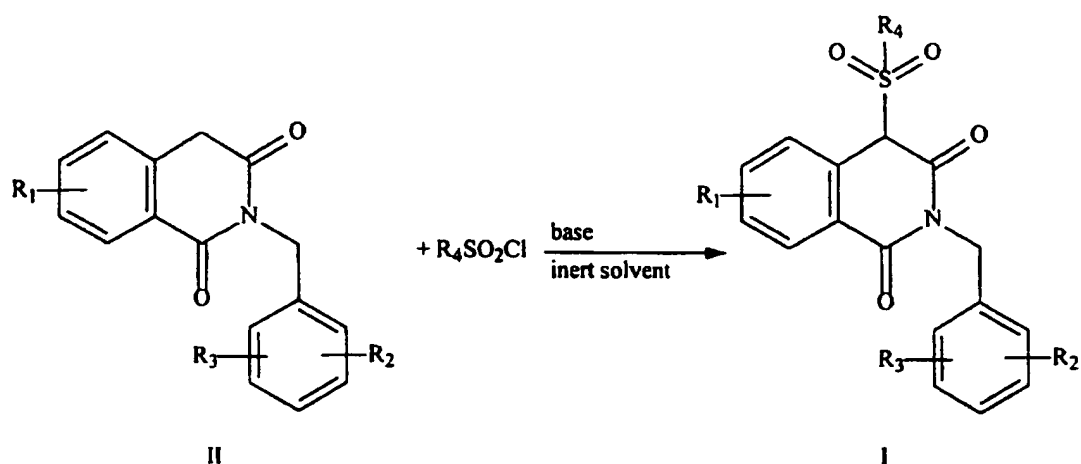
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R₂ is hydrogen;

R₃ is hydrogen, fluorine, chlorine, bromine; trifluoromethyl, C₁₋₄ alkyl or C₁₋₄ alkoxy; and,

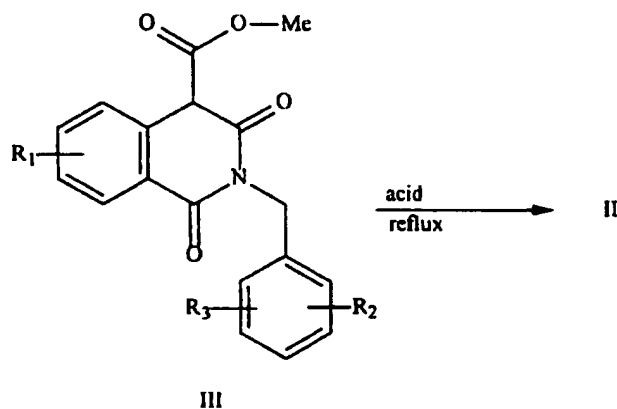
30 R₄ is isopropyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl monosubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro.

In accordance with a preferred method, the compounds of the invention may be prepared by reaction of a suitably substituted 2-benzyl-4H-isoquinoline-1,3-dione (II) with an alkyl or
35 aryl sulfonyl halide in the presence of a base, such as, for example, 1,8-diazabicyclo[5.4.0]undec-7ene (DBU), in an inert solvent, such as, for example, methylene chloride, as illustrated by the reaction scheme shown below.



The intermediate II can be prepared by hydrolysis and decarboxylation of the corresponding ester III (the methyl ester is shown, but any ester is suitable) for example by heating with an acid such as 48% HBr.

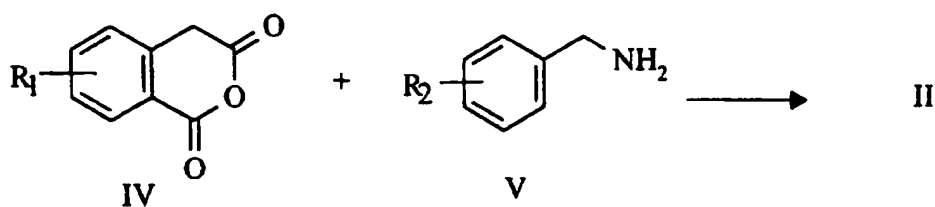
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Esters of formula III are known and their preparation is described in the chemical literature (e.g. M.S. Malamas et al., J. Med. Chem. 1994, 37, 2043)

10

Alternatively II may be prepared by reaction of a suitably substituted homophthalic anhydride (IV) with a suitably substituted benzyl amine (V) in an inert solvent such as toluene.



15

Synthetic Examples

The following examples describe the synthesis of specific compounds in accordance with the invention.

5

Example 1

2-Benzyl-6-chloro-4-(1-methylethyl)sulfonyl-4H-isoquinolin-1,3-dione

Isopropylsulfonyl chloride (140 mg, 0.962mmol) was added to a solution of 250 mg (0.875 mmol) 2-benzyl-6-chloro-4H-isoquinoline-1,3-dione and 270 mg (1.75 mmol) DBU in 2.5 mL methylene chloride under Argon, which was cooled in ice-EtOH to -10°C. After 30 min, the reaction was allowed to warm to room temperature and was stirred overnight. The reaction was diluted with EtOAc, washed three times with 2N HCl, dried (Na₂SO₄) and concentrated. The residue was triturated with EtOH, petroleum ether was added and the resulting crystals were filtered. Recrystallization from MeOH-petroleum ether gave 186 mg of the title compound, mp 150-152°C.

15

Example 2

2-(2-Fluorobenzyl)-4-(1-methylethyl)sulfonyl-4H-isoquinoline-1,3-dione

A mixture of 800 mg (4.9 mmol) homophthalic anhydride, 680 mg (5.4 mmol) 2-fluorobenzylamine and 500 mg 4Å molecular sieves in 1.5 mL toluene was stirred and heated at reflux overnight. A solution of 30% MeOH in CH₂Cl₂ was added, the resulting hot mixture filtered and the filtrate concentrated to give 900 mg 2-(2-fluorobenzyl)-4H-isoquinoline-1,3-dione, mp 140-144°C. A 500 mg (1.86 mmol) portion of this product was combined with 570 mg (3.71 mmol) DBU in 5 mL CH₂Cl₂ under argon, and cooled to -10°C. Isopropylsulfonyl chloride (290 mg, 2.04 mmol) was added, and after stirring 15 min the reaction was allowed to warm to room temperature. After 4 hr the reaction was diluted with EtOAc and worked up as in Example 1 giving 329 mg of the title compound, mp 174-181°C.

25

The compounds described in Table 1 were made in an analogous fashion to that described in Examples 1 and 2.

30

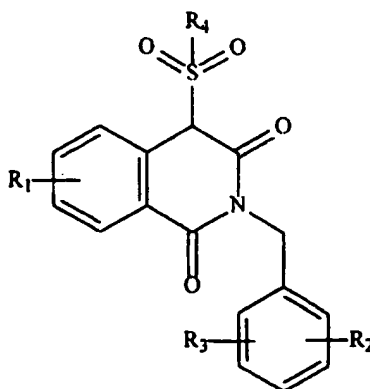


Table 1					
Example	R ₁	R ₂	R ₃	R ₄	mp (°C)
3	H	H	H	n-propyl	147-149
4	H	H	H	n-butyl	127-129
5	H	H	H	isopropyl	210-213
6	H	3-Cl	H	isopropyl	157-160
7	H	4-Cl	H	isopropyl	145-149
8	H	4-F	H	isopropyl	137-141
9	H	3-F	4-F	isopropyl	129-133
10	6-Cl	3-F	4-F	isopropyl	145-146
11	H	H	H	1,1,1-trifluoroethyl	170-200 dec.
12	H	H	H	phenyl	181-184
13	H	H	H	4-bromophenyl	233-236
14	H	H	H	4-methylphenyl	192-196
15	H	H	H	2-naphthyl	195-200
16	H	H	H	4-methoxyphenyl	142-146
17	H	H	H	4-(t-butyl)phenyl	150-153
18	H	H	H	4-fluorophenyl	211-214
19	H	H	H	4-chlorophenyl	237-240
20	H	H	H	4-nitrophenyl	245-248
21	H	H	H	2-thienyl	234-237

Biological Properties

- 5 As mentioned above, the above described compounds of formula I or IA are useful as antiinflammatory agents, by virtue of their ability to inhibit both COX-1 and COX-2 approximately equipotently or, in the case of certain preferred compounds, to inhibit COX-2 to a significantly greater extent than COX-1.
- 10 The degree to which compounds inhibit COX-1 and COX-2 can be determined using the *in vitro* microsomal and cell assay techniques described below.

Microsomal Assay. Human cyclooxygenase 1 and 2 are expressed in a baculovirus expression system using High 5 insect cells. Microsomal fractions prepared from the cells are stored at -80°C. The assays are performed at room temperature in phosphate buffered saline. After incubating the COX-1 or COX-2 microsomes with hematin (2 µM), phenol (0.5 mM) and reduced glutathione (1 mM) for 5 minutes, inhibitor or DMSO vehicle is added and allowed to incubate for 20 minutes. Arachidonic acid (2 µM) is added and after 20 minutes the reaction is stopped by the addition of HCl (0.1 N HCl, final concentration). Samples are then diluted in EIA buffer containing 25 µM indomethacin (final concentration) and assayed for PGE₂ using Amersham PGE₂ EIA extended range protocol (RPN 222).

Cell Assay. Cos-A2 cells stably transfected with human recombinant COX-1 or COX-2 are cultured in 96 well tissue culture plates with Dulbecco's Modified Eagle Medium supplemented with 10% fetal bovine serum, glutamine (2 mM), penicillin (50 U/mL), streptomycin (50 mg/mL) and geneticin (400 µg/mL). Media is removed from confluent monolayers and the cells are washed twice with Hank's buffered saline solution. Fresh HBSS is added, with or without inhibitor, and the cells are incubated for 30 minutes at 37°C. Arachidonic acid (30 µM) is then added and the cells are incubated for an additional one hour at 37°C. Individual experiments represent a mean of triplicate wells for control and inhibitor doses. Supernatants are removed and stored at -80°C until assayed for PGE₂ by EIA (Amersham).

The inhibitory activities against COX-1 and COX-2 of the compounds described in the above Synthetic Examples were determined using the two in vitro assays described above. The results of these tests are given in Tables 2 and 3.

Table 2						
% Inhibition of COX Enzymes in Microsomal Assays						
Cmpd. of Example	COX-2			COX-1		
	concentration of test compound (μgrams/mL)					
	10	1	0.1	10	1	0.1
1	97	87	34	57	34	10
2	49	37	10	18	14	-1
3	27	15	-6	33	22	-9
4	20	30	0	15	15	4
5	58	56	27	23	11	-6
6	27	27	10	30	19	-10
7	67	62	3	36	4	-3
8	86	68	-1	47	28	11
9	80	75	8	57	17	10
10	100	100	-3	96	40	13
11	52	32	23	50	21	4
12	72	58	22	74	59	17
13	100	92	28	100	74	44
14	100	63	-13	100	93	59
15	34	14	-29	57	24	23
16	97	74	21	93	81	33
17	39	12	20	45	20	17
18	81	66	33	92	76	48
19	93	89	59	89	71	52
20	46	37	20	62	41	21
21	48	46	12	67	14	17

Table 3								
Inhibition of COX Enzymes in COS Cell Assays								
Cmpd. of Example	COX-2				COX-1			
	% inhibition at 10, 1 and 0.1 μ M			IC ₅₀ (μ M)	% inhibition at 10, 1 and 0.1 μ M			IC ₅₀ (μ M)
5	51	37	17	--	74	43	13	--
7	74	52	26	--	72	46	6	--
2	46	45	NT	--	39	33	NT	--
8	--	--	--	0.09	--	--	--	0.25
9	--	--	--	0.2	--	--	--	0.57
1	--	--	--	0.06	--	--	--	1.4
10	--	--	--	0.1	88	55	20	--
11	30	0	NT	64	64	0	NT	--
12	65	48	39	--	85	61	22	--
21	89	80	65	--	94	67	35	--

NT = not tested

5 The antiinflammatory activities of two compounds in accordance with the invention (those of Examples 1 and 10) were determined in vivo and compared to those of the known antiinflammatory agents indomethacin and meloxicam, using the Carrageenan-Induced Paw Edema in Rats protocol described by C.A Winter et al. *J. Pharmacol. Exp. Ther.* 1963, 141, 369. Test compounds were administered orally. The results of this testing are reported in Table 4.

10

Table 4		
Effect of Compounds in Carrageenan Paw Edema in Rats		
Compound	Dose (mg/kg)	% Inhibition
Ex. 1	30	42.5*
Ex. 10	30	38.6*
Indomethacin	10	58*
Meloxicam	30	56*

* p < 0.05

The compounds of the present invention are useful for the treatment of inflammation. Such use constitutes another aspect of the invention.

The compounds of the invention (compounds of formula I or IA) may be administered by the oral, parenteral or rectal routes, as active ingredients in customary dosage unit compositions, that is, compositions in dosage unit form comprising an inert pharmaceutical carrier and one effective dosage unit of the active ingredient, such as tablets, coated pills, capsules, wafers, powders, solutions, suspensions, emulsions, syrups, suppositories and the like. One effective oral dosage unit of the compounds according to the present invention is from 0.03 to 7.5 mg/kg body weight, preferably 0.08 to 1.5 mg/kg body weight. The daily dose rate is from 0.08 to 15.0 mg/kg, preferably 0.16 to 3.0 mg/kg.

The compounds of the invention may be administered either alone or in combination with other antiinflammatory agents.

Another aspect of the invention constitutes the preparation of pharmaceutical dosage forms suitable for administration of compounds in accordance with the invention. The following Pharmaceutical Examples describe the preparation of representative pharmaceutical dosage forms. These examples are not intended to limit the scope of the invention. Those skilled in the art will understand how other formulations can be made.

Pharmaceutical Examples

Example A

Tablets

The tablet composition is compounded from the following ingredients:

Ingredient	Parts
Compound of Ex. 1	10.0
Corn Starch	112.0
Polyvinylpyrrolidone	175.0
Magnesium Stearate	3.0
Total	300.0

Preparation:

The active ingredient and the corn starch are intimately admixed with each other, the mixture is moistened with an aqueous 14% solution of the polyvinylpyrrolidone, and the moist mass is granulated through a 1.5 mm-mesh screen. The moist granulate is dried at 45 °C. and again passed through the screen, admixed with the magnesium stearate, and the mixture is compressed into 300 mg tablets. Each tablet is an oral dosage unit composition containing 10 mg of the active ingredient.

EXAMPLE B**Coated Pills**

- The pill core composition is compounded from the following ingredients:

Ingredient	Parts
Compound of Example 1	10.0
Corn starch	260.0
Gelatin	8.0
Talcum	18.0
Magnesium stearate	4.0
Total	300.0

Preparation:

The active ingredient and the corn starch are intimately admixed with each other, the mixture is moistened with an aqueous 10% solution of the gelatin and the moist mass is granulated through a 1.5 mm-mesh screen. The moist granulate is dried at 45 °C., again passed through the screen, admixed with the talcum and the magnesium stearate, and the composition is compressed into 300 mg pill cores which are subsequently coated with a thin shell consisting essentially of a mixture of talcum and sugar, and finally polished with beeswax. Each coated pill is an oral dosage unit composition containing 10 mg of the active ingredient.

EXAMPLE C**Gelatin Capsules**

- 5 The capsule filler composition is compounded from the following ingredients:

Ingredient	Parts
Compound of Example 1	5.0
Corn starch	385.0
Colloidal silicic acid	6.0
Magnesium stearate	4.0
Total	400.0

Preparation:

- 10 The ingredients are intimately admixed with each other by milling, and 400 mg portions of the mixture are filled into No. 1 gelatin capsules. Each capsule is an oral dosage unit composition containing 5 mgm of the active ingredient.

EXAMPLE D

15

Suppositories

The suppository composition is compounded from the following ingredients:

Ingredient	Parts
Compound of Example 1	25.0
Suppository base (e.g. cocoa butter)	1725.0
Total	1750.0

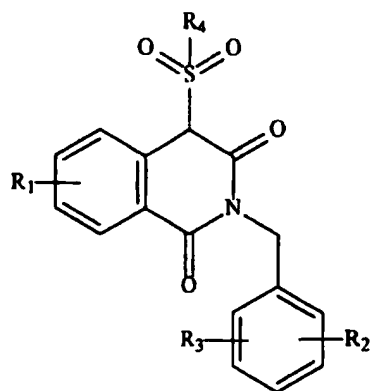
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Preparation:

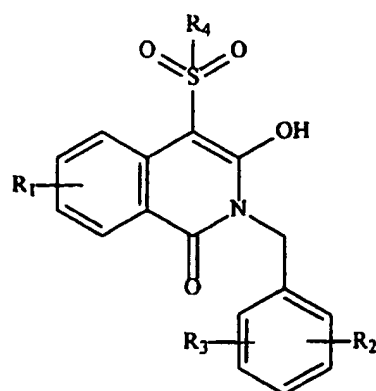
- 25 The finely pulverized active ingredient is homogeneously blended with the aid of an immersion homogenizer into the suppository base which had been melted and cooled to 40 ° C. The composition is cooled to 38 °C., and 1.75 gm portions thereof are poured into cooled suppository molds and allowed to harden therein. Each suppository is a rectal dosage unit composition containing 25 mg of the active ingredient.

We Claim:

1. A compound of the formula I or IA



(I)



(IA)

wherein,

10 R₁ is hydrogen, halogen, C₁₋₄ alkyl, or C₁₋₄ alkoxy;

R₂ and R₃ are the same or different and each is hydrogen, halogen, trifluoromethyl, C₁₋₄ alkyl, or C₁₋₄ alkoxy; and,

15 R₄ is C₃₋₄ alkyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, trifluoromethyl, or nitro.

2. A compound of formula I or IA, in accordance with claim 1, wherein:

20

R₁ is hydrogen, or is in the 6- or 7-position and is fluorine, chlorine, bromine, C₁₋₄ alkyl or C₁₋₄ alkoxy;

25 R₂ and R₃ are the same or different and each is hydrogen, fluorine, chlorine, bromine; trifluoromethyl, C₁₋₄ alkyl or C₁₋₄ alkoxy; and,

R₄ is isopropyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl mono- or disubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro.

30

3. A compound of formula I or IA, in accordance with claim 2, wherein:

R₁ is hydrogen, or is in the 6- or 7-position and is fluorine, chlorine, bromine, C₁₋₄ alkyl or C₁₋₄ alkoxy;

5

R₂ is hydrogen;

R₃ is hydrogen, fluorine, chlorine, bromine; trifluoromethyl, C₁₋₄ alkyl or C₁₋₄ alkoxy; and,

10 R₄ is isopropyl, 1,1,1-trifluoroethyl, 2-thienyl, 2-naphthyl, phenyl or phenyl monosubstituted with C₁₋₄ alkyl, C₁₋₄ alkoxy, fluorine, chlorine, bromine, trifluoromethyl, or nitro.

4. A compound selected from the group consisting of:

15

2-Benzyl-6-chloro-4-(1-methylethyl)sulfonyl-4H-isoquinolin-1,3-dione; and,

2-(2-Fluorobenzyl)-4-(1-methylethyl)sulfonyl-4H-isoquinoline-1,3-dione.

20

5. A method for treating inflammation which comprises administering to a host in need of such treatment an antiinflammatory amount of a compound in accordance with claim 1, 2, 3 or 4.

25

6. A pharmaceutical composition comprising a compound in accordance with claim 1, 2, 3 or 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07980**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :CO7D 217/24; A61K 31/47

US CL :546/142; 514/309

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/142; 514/309

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS COMPUTER SEARCH 1966 - TO DATE**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,233,299 A (TRUMMLITZ et al) 11 November 1980, see entire document.	1-6
A	JP 07118236 A2 (HOKKO CHEM IND CO) 09 MAY 1995, see entire document.	1-4



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

24 JUNE 1997

Date of mailing of the international search report

12 AUG 1997

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